

**REMARKS**

The Office Action, the cited and applied references and the Notice of Non-Responsive Amendment dated April 6, 2009, have been carefully reviewed. No claim is allowed. Claims 1, 3, 5, 11-44, 47-53, 58 and 59 presently appear in this application, with claims 58 and 59 newly added to replace claims 56 and 57 that are "not entered", and define patentable subject matter warranting their allowance.

Reconsideration and allowance are hereby respectfully solicited.

In the Notice of Non-Responsive Amendment mailed April 9, 2008, the examiner holds that since applicants have received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, the examiner states that after entry of the amendment, all remaining claims would be withdrawn from the consideration as being directed to non-elected inventions, and therefore the amendment, which presents only claims drawn to non-elected inventions, is non-responsive and will not be entered. The amendments to the specification and claims and the remarks below are responsive to the Office Action of June 29, 2007, which has been carefully reviewed.

The disclosure has been objected to because of improperly demarcated trademark appearing in the specification. The specification is now amended to refer to GenBank as "GenBank®", thereby obviating part of this objection.

Regarding the part of the objection to hyperlinks and/or other forms of browser-executable code embedded in the specification,

this part of the objection is obviated by the amendment to page 18 to disclose merely a URL address. MPEP §608.01 VII states that examples of a hyperlink as a browser-executable code prohibited by 37 C.F.R. §1.57(d) are "a URL placed between these symbols '<>' and http:// followed by a URL address. As amended, the URL address on page 18 is no longer a hyperlink or browser-executable, as http:// is not present and the symbols "<>" are not used. URL's, such as now at page 18, are permissible.

Reconsideration and withdrawal of the objection are therefore respectfully requested.

Claims 1-55 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The examiner holds that the specification only adequately describes polypeptides that allow the anchorage of the  $\beta_2$ -microglobulin molecule to the cell membrane wherein the polypeptide comprises the transmembrane and cytoplasmic domain from the MHC I class heavy chain of HLA-A2 which has the amino acid sequence of SEQ ID NO: 2 or wherein the polypeptide comprises the transmembrane and cytoplasmic domain of the human CD3 $\zeta$  polypeptide. The examiner continues by stating "Furthermore, the specification does not adequately describe the genus of peptides comprising at least one antigenic peptide comprising a MHC class I epitope, wherein said antigenic peptide is not related to an autoimmune disease and only adequately describes antigenic peptides comprising a MHC class I epitope, wherein the peptide has a defined amino acid sequence in the specification (see for example pages 15-17

that discloses SEQ ID NOS giving the amino acid sequence of known MHC class I epitopes." This rejection is respectfully traversed.

Applicants respectfully disagree with the examiner that the specification only adequately describes the very narrow scope of polypeptides that allow the anchorage of the  $\beta_2$ -microglobulin molecule to the cell membrane acknowledged by the examiner. A person having ordinary skill in the art of biochemistry would have no reason to question the assumption that if the transmembrane and cytoplasmic domain from the MHC I class heavy chain of HLA-A2, which has the amino acid sequence of SEQ ID NO:2, can be successfully used in the invention as shown in the Examples, then any other transmembrane polypeptide with a cytoplasmic tail could fill the same function of anchoring the polypeptide to the cell membrane.

In fact, in Example 5 in the present specification, it is also shown that a fusion polypeptide comprising CD40 transmembrane and cytoplasmic portion successfully anchors the polypeptide to the cell membrane. Since polypeptides as different as CD40 and HLA-A2 are shown in the present specification to be capable of exerting the same function of anchoring the polypeptide to the cell membrane, there can be little doubt that any other transmembrane polypeptide with a cytoplasmic tail could fill the same function.

Although applicants respectfully disagree with the examiner, applicants agree to amend claim 1 in order to advance prosecution by reciting "at least one antigenic peptide comprising a MHC class I epitope selected from a tumor-associated antigen (TAA), an antigen from a pathogen selected from a bacterial, a viral, a fungal and a parasite

antigen, and at least one idiotypic peptide expressed by autoreactive T lymphocytes, wherein said polypeptide stretch at the  $\beta_2$ -microglobulin carboxyl terminal consists of a bridge peptide which spans the whole distance to the cell membrane, said bridge peptide being linked to a sequence which can exert the required anchoring function, consisting of the full or partial transmembrane and/or cytoplasmic domain of a molecule selected from the group consisting of the human CD3  $\zeta$  polypeptide, the MHC I class heavy chain of HLA-A, HLA-B or HLA-C molecule and CD40." New independent claim 58, corresponding to claim 1 but limited to polypeptides that allow the anchorage of the  $\beta_2$ -microglobulin molecule to the cell membrane selected from CD3  $\zeta$  polypeptide and the MHC I class heavy chain of HLA-A2 and antigenic peptides as supported on pages 15-17 in the description and which are considered by the examiner to be adequately described in the specification, are added. New independent claim 59 is identical to claim 58, but further defines CD40 as a polypeptide that allows anchorage and an HIV-peptide as an antigenic peptide. Support for functional expression of CD 40 is found in the specification on page 44, lines 13-19, and support for the HIV-peptide is found in the specification on page 20, lines 1-2 and in claim 25.

In conclusion, the present claims do indeed comply with the written description requirement and reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1-55 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The examiner recites the factors considered *In re Wands* when determining if

the disclosure satisfies the enablement rejection. The examiner states "it is noted that the specification has not adequately described DNA vaccines, cellular vaccines or pharmaceutical compositions comprising said polynucleotides for the prevention and treatment of cancer or diseases caused by pathogenic organisms, nor has it adequately described the methods of immunizing mammals to treat or prevent cancer or diseases caused by pathogenic organisms. Notably, the specification only provides evidence that antigen specific CTLs can be generated with a construct comprising as a MHC class I epitope amino acids 257-264 of chicken ovalbumin and therefore does not provide any evidence that applicant was in possession of using the claimed polynucleotides directed to tumor antigens or pathogenic organism antigens as a DNA vaccination, a cellular vaccination or any pharmaceutical composition for the prevention and treatment of cancer or diseases caused by pathogenic organisms. Notably, one of skill in the art would not consider the ability of a construct to generate antigen specific CTLs as representative of the construct's ability to be a DNA vaccine, a cellular vaccine or any pharmaceutical composition for the prevention and treatment of cancer or diseases caused by pathogenic organisms."

The examiner holds that the specification only provides evidence that antigen specific CTLs can be generated with a construct comprising as an MHC class epitope amino acids 257-264 of chicken ovalbumin and therefore one of skill in the art would be subject to undue and unreasonable experimentation to use the claimed products in methods of preventing and treating diseases. The examiner then concludes "...since the specification provides no working examples

wherein the claimed products prevent or treat any diseases and merely provide prophetic examples that only give general guidance as to how to use the claimed product to prevent or treat diseases on pages 23-31, the specification is not deemed sufficient to enable the claims." The examiner is also of the opinion that "... at the time the instant application was filed, the state of the art indicated that DNA and cellular vaccines for the prevention and treatment of diseases was highly unpredictable in the art." The examiner further alleges that "...it is noted that preventing cancer or infection is intractable, if not impossible..." This rejection is respectfully traversed.

Applicants would like to point out that vaccines have been used for more than a hundred years to prevent diseases. Obviously, the vaccines commonly in use today do not prevent infection of cells, but prevent disease by preventing the infectious agent from multiplying and spreading in the host. Also, the present application does not claim a vaccine for preventing infection, but rather for prevention, inhibition or treatment of a disease.

The examiner has cited 14 different documents, most of which were cited to support the examiner's allegation of "the unpredictability of the art." For example, an experiment in Margalit et al. (the inventors in the present application) is cited, in which cells expressing the low-affinity TRP-2<sub>181-188</sub> peptide elicited potent CTLs and induced protective anti-melanoma immunity but failed to suppress the growth of pre-established tumors. The examiner however appears to have missed the authors' explanation of this apparent paradox, that the initial administration of MO5 cells (a spontaneous

murine B16 melanoma) in a non-immunostimulatory context may have enhanced the activity of regulatory T cells (Tregs) to a level that prevented later induction of TRP-2-specific CTLs by the transformed antigen presenting cells expressing the polypeptide of the invention. The antigen presenting cells used in the experiment disclosed in the cited Margalit et al. publication, the RMA-S cells, are not true dendritic cells and do not possess all the faculties of dendritic cells such as the capability to down-regulate Tregs. Thus, the failed suppression of tumor growth in this case was the consequence of the specific experimental circumstances and not of an intrinsic feature of the cellular vaccine used.

In another document cited by the examiner, Lollini et al. teach that "most current tumor antigens appear to be unsuitable targets for cancer immunoprevention" since most do not have "crucial pathogenic role in tumor growth" and/or are ineffective to stimulate both arms of the immune system. Bodey et al. is cited by the examiner to show that some tumors may evade the immune attack elicited by the vaccine by a natural selection process that leads to the selective enrichment of clones of highly aggressive neoplastically transformed cells, which apparently are so dedifferentiated that they no longer express cancer cell specific molecules. Applicants would like to draw the examiner's attention to the fact that a method causing very efficient killing of the tumor cells would leave no time for a natural selection process to take place.

The examiner thus cites failed attempts in the past to argue that the present invention cannot possibly succeed. However, the

present invention introduces a new mechanism of presenting the (tumor) specific antigen, which is many times more efficient than the naturally existing mechanism used in all past attempts to produce active specific immunotherapy for cancer. The present specification discloses the advantages of the present invention on page 11, lines 5-12 of the present specification as follows:

Duration of the functional MHC class I/peptide complex on the cell surface is governed by the affinity of the peptide for the MHC molecule. Dissociation of the peptide from its binding groove in the  $\alpha$  heavy chain, results in practically irreversible disruption of the ternary complex formed between the  $\alpha$  chain,  $\beta_2m$  and peptide. Both latter components are not anchored to the cell membrane and immediately detach from the cell, while the  $\alpha$  chain is later internalized. Stabilization of a particular class I/peptide complex by enabling fast re-association is therefore likely to result in high level of presentation of the antigenic peptide.

Attached hereto from the examiner's consideration is a 1.132 declaration executed by Dr. Gideon Gross to present the results of two experiments recently conducted by the present inventors and published in the *Journal of Immunology*, 2006, 176: 217-224. The first experiment shows that mice challenged with MO5 cells, chicken ovalbumin-transfected variant of the spontaneous murine B16 melanoma, were successfully treated by immunization with a vaccine of the present invention directed to the antigenic chicken ovalbumin peptide.

The second experiment shows that mice immunized with the presently claimed vaccine and then challenged with MO5 cells are protected from the growth of the MO5 tumors. Here, two antigenic peptides are used that are expressed by the MO5 cells; chicken ovalbumin and TRP- $2_{181-188}$ , a native tumor associated antigenic peptide of the MO5 cells. The model system used in the second experiment

employed two very different antigenic peptides, ectopically expressed chicken ovalbumin and the native tumor associated antigen TRP-2. Thus, applicants have now provided evidence of a relationship between the structure of the invention and its function, which would permit one skilled in the art to immediately envisage the product claimed for the disclosed process.

The exceptionally high efficiency of antigen presentation in antigen presenting cells expressing the polypeptides of the present invention makes the comparison with cellular vaccines disclosed in the documents cited by the examiner irrelevant since those vaccines are inherently inferior to those of the present invention, especially in view of the new results presented in the attached declaration.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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